The NEW ENGLAND JOURNAL of MEDICINE

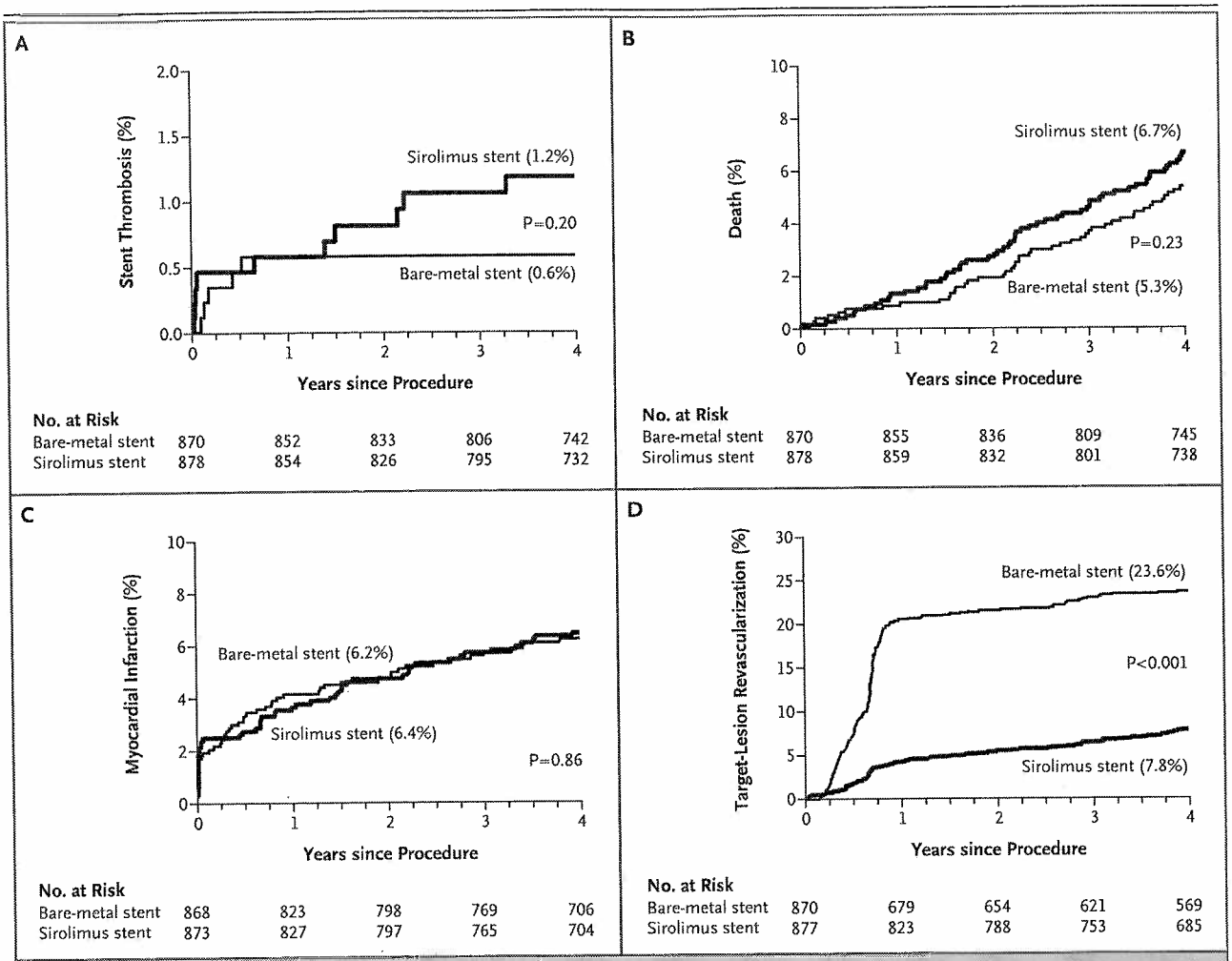

Figure 1. Kaplan–Meier Curves Representing the Estimated 4-Year Cumulative Incidence Rates of Stent Thrombosis, Death, Myocardial Infarction, and Target-Lesion Revascularization for the Pooled Randomized Trials of Sirolimus-Eluting Stents and Bare-Metal Stents.

The number of patients at risk each year is provided, equal to the number of patients for whom follow-up data were available at each time minus those with earlier events. The median duration of follow-up was 4.0 years.

eluting–stent groups and bare-metal–stent group at all prespecified time periods, except that there were significantly fewer myocardial infarctions in the paclitaxel-stent group than in the bare-metal–stent group between 30 days after implantation and 1 year (0.8% vs. 1.8%, P=0.01).

There were no differences in the 4-year composite rates of death or myocardial infarction, death or Q-wave myocardial infarction, or myocardial infarction or death from cardiac causes between either drug-eluting stent and its control (Table 3) or at any interval time period (Supplementary Appendix), except that between 30 days after implantation and 1 year, the composite rate of myocardial infarction or death from cardiac causes was lower in the paclitaxel-stent group than in the bare-metal–stent group (1.4% vs. 2.5%, P=0.03). This reduction in rate was driven by a lower rate of non–Q-wave myocardial infarction in the paclitaxel-stent group than in the bare-metal–stent group (0.4% vs. 1.6%, P<0.001).

DISCUSSION

We performed a patient-level pooled meta-analysis of four randomized, double-blind trials of sirolimus-eluting stents versus bare-metal stents and five randomized, double-blind trials of paclitaxel-eluting stents versus bare-metal stents in single, previously untreated coronary lesions through

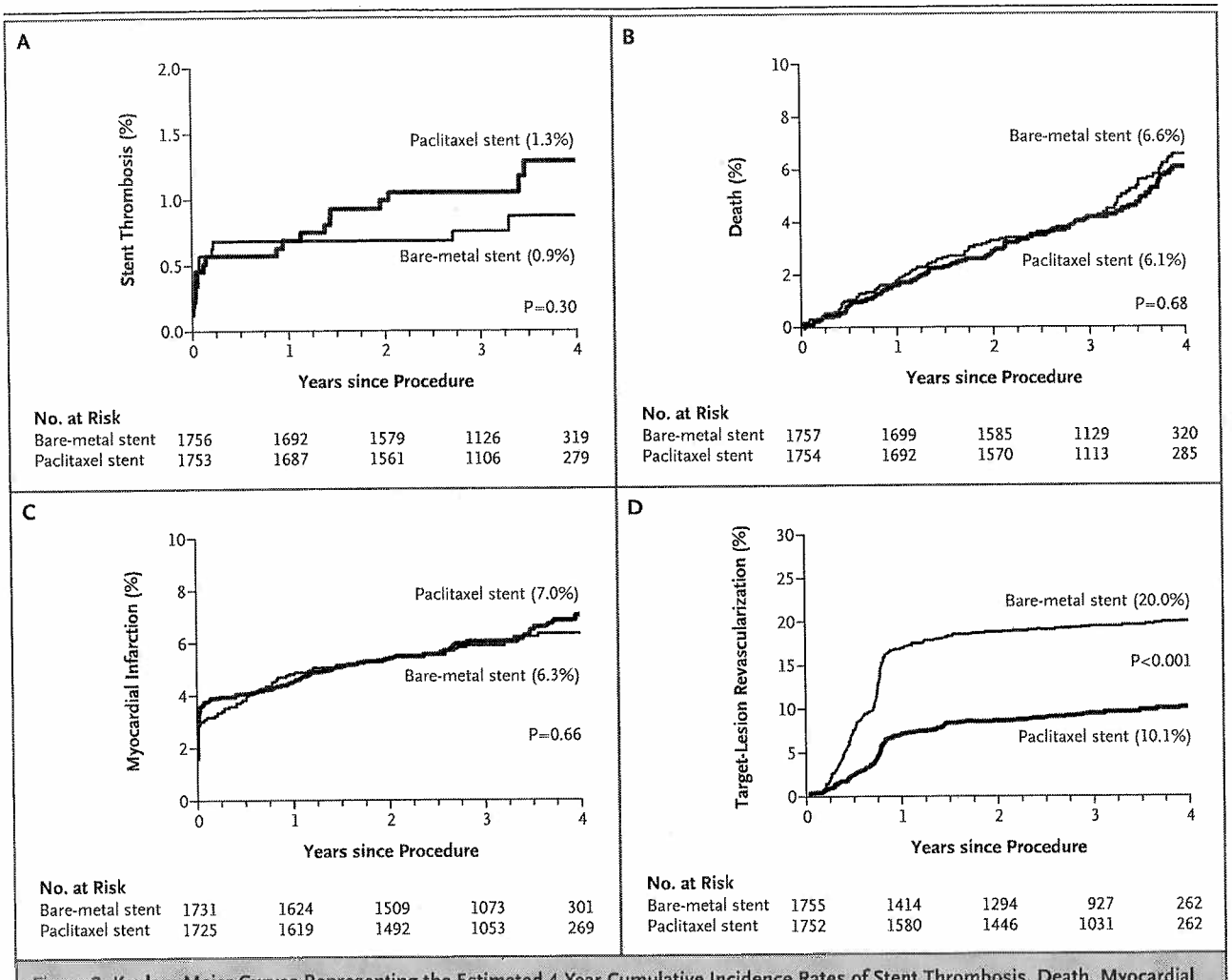

Figure 2. Kaplan–Meier Curves Representing the Estimated 4-Year Cumulative Incidence Rates of Stent Thrombosis, Death, Myocardial Infarction, and Target-Lesion Revascularization for the Pooled Randomized Trials of Paclitaxel-Eluting Stents and Bare-Metal Stents.

The number of patients at risk each year is provided, equal to the number of patients for whom follow-up data were available at each time minus those with earlier events. The median duration of follow-up was 3.2 years

4 years of follow-up. The principal findings were that although the overall rates of stent thrombosis were not significantly increased with drug-eluting stents, both sirolimus-eluting stents and paclitaxel-eluting stents were associated with a small but significant increase in the incidence of late stent thrombosis between 1 and 4 years after implantation. In addition, both drug-eluting stents were associated with marked reductions in ischemic target-lesion revascularization and target-vessel revascularization, an advantage that was maintained through 4 years of follow-up. The rates of death or myocardial infarction were not significantly different between the groups with drug-eluting stents and the control groups, either at 4 years of follow-up or between 1 and 4 years.

The number of episodes of stent thrombosis within the first year were identical among patients with sirolimus-eluting stents and those with bare-metal stents (5 patients with episodes in each group) and among patients with paclitaxel-eluting stents and those with bare-metal stents (12 patients in each group). Between 1 and 4 years, however, there were modest increases in stent thrombosis in both groups with drug-eluting stents, as compared with the control groups (14 patients with episodes in the groups with drug-eluting stents vs. 2 patients in the bare-metal–stent groups — a finding that is consistent with

approximately one extra stent thrombosis per 500 patient-years of treatment with drug-eluting stents). Although our study does not identify the potential causes of late stent thrombosis, possible causes include delayed or incomplete endothelialization, late polymer reactions, strut fractures, positive remodeling with stent malapposition with or without aneurysm formation, and new plaque rupture either adjacent to or within the stented site, among others.[10-13,18,19]

Our study also demonstrates a marked and persistent reduction in target-lesion revascularization and target-vessel revascularization with both drug-eluting stents, as compared with bare-metal stents. The maximal difference between drug-eluting stents and bare-metal stents in clinical restenosis occurred by 1 year, with the hazard curves remaining parallel between 1 and 4 years. In this regard, the durability of clinical efficacy for drug-eluting stents during late follow-up stands in contradistinction to the "catch-up" phenomenon of late restenosis noted after coronary brachytherapy.[20,21] Although the performance of routine angiographic follow-up may have increased the absolute difference in the rates of clinical restenosis between drug-eluting stents and bare-metal stents, the relative benefit is unlikely to have been affected.[22]

No significant differences in the cumulative 4-year rates of death or myocardial infarction were observed between patients receiving either drug-eluting stents or bare-metal stents. It is possible that reductions in the rates of death or myocardial infarction that otherwise might result from prevention of restenosis by drug-eluting stents may be offset by adverse events resulting from late stent thrombosis. In-stent restenosis presents as acute myocardial infarction in 3.5 to 19.4% of patients[23-26] and as such is not always a benign process. However, the majority of episodes of stent thrombosis present as death or myocardial infarction.[27,28] Thus, a large reduction in a phenomenon with moderate clinical risk (restenosis) may be offset by a small increase in a phenomenon with high clinical risk (stent thrombosis).

It is important to note that stent thromboses occurring subsequent to any target-lesion revascularization were excluded from the counts of episodes of stent thrombosis in most of the trials (see the definitions of stent thrombosis in the Supplementary Appendix).[29] The purpose of this exclusion was to ensure that only episodes of stent thrombosis related to the original stent were included. However, the procedures to treat restenosis (balloon angioplasty, brachytherapy, or additional stenting) may result in "secondary" episodes of stent thrombosis. Such secondary stent thromboses would be expected to be more common with bare-metal stents, since revascularization procedures are much more common with these stents. Indeed, in an unpublished analysis, when such secondary episodes were considered, no overall or late differences in the patient-level rates of stent thrombosis between drug-eluting stents and bare-metal stents were present.[29] Since data regarding death and myocardial infarction were not censored after target-lesion revascularization, greater rates of restenosis and secondary thrombosis with bare-metal stents than with drug-eluting stents probably contributed to the similar observed overall rates of death and myocardial infarction between the stent types in our analysis. Given the difficulties in defining stent thrombosis in the absence of angiographic confirmation or results on autopsy, greater emphasis should be placed on the occurrence of death and myocardial infarction, in our opinion, rather than on stent thrombosis, as indicative of the overall safety profile of a coronary intervention. Moreover, given the observation that the directional effect of drug-eluting stents on subsequent stent thrombosis, revascularization, death, and myocardial infarction may vary, we believe that composite measures combining safety and efficacy end points should be avoided in future trials of antirestenotic devices.

Our findings differ from those of some other investigators, who have suggested, on the basis of trial-level meta-analyses, that overall rates of stent thrombosis and death are higher with drug-eluting stents than with bare-metal stents.[16,17] These discrepancies may be partially explained by the fact that we had access to the complete patient-level data from the trials we examined and did not have to rely on an estimation of event rates from limited published results, abstracts, and online summaries. We also confined our analysis to a precisely defined subgroup of clinical trials involving drug-eluting stents, whereas some previous analyses have also included later studies that were not double-blind.[16]

Several limitations of our analysis deserve comment. First, given the relatively infrequent occurrence of death, myocardial infarction, and stent thrombosis, larger studies with longer-term fol-

low-up are required to detect small differences in event rates. Moreover, we made no adjustments for the multiple end points examined. The interval data analyses in particular should be considered hypothesis-generating. Second, our analysis is most applicable for patients with single, previously untreated coronary lesions, as reflected in the labels for sirolimus-eluting stents (lesions as long as 30 mm in vessels of 2.5 to 3.5 mm in diameter) and paclitaxel-eluting stents (lesions as long as 28 mm in vessels of 2.5 to 3.75 mm in diameter) that were approved by the Food and Drug Administration. The rates of stent thrombosis and the relative risk–benefit ratio of drug-eluting stents versus bare-metal stents may vary in the "real world," in which stents are implanted in more complex scenarios (i.e., "off-label" use).[27,28] Third, the nine studies we analyzed used different clinical sites, adjudication committees, and core laboratories, with possible differences in definitions and processes. Fourth, the paclitaxel-stent trials included both the commercial slow rate–release formulation and the noncommercialized moderate rate–release formulation. However, the results were directionally similar with both devices, and no major differences have been described between the two versions of this stent.[6] Fifth, in five of the trials, the protocol-specified definitions of stent thrombosis after 30 days required angiographic confirmation and may therefore underestimate the true event rate. Sixth, pooling of the data from sirolimus-stent trials and paclitaxel-stent trials was avoided, since the mechanisms underlying the safety and efficacy of these two types of stents may differ. Given the different entry criteria for types of lesions in the two groups of trials, as well as the different bare-metal stents used as controls, comparisons across the two pooled meta-analyses may not be valid. Finally, detailed data regarding the use of antiplatelet medication throughout the follow-up period were not available, precluding firm recommendations regarding the optimal duration of thienopyridine administration.

In conclusion, our study examined the relative safety and efficacy of drug-eluting stents, as compared with bare-metal stents, in a pooled, patient-level analysis of double-blind, randomized trial data. The use of both sirolimus-eluting stents and paclitaxel-eluting stents was associated with a small but significant increase in the incidence of late stent thrombosis between 1 and 4 years after implantation, as compared with that of bare-metal stents. We also reconfirmed the marked benefit of both types of drug-eluting stents in reducing the need for subsequent revascularization procedures, with persistence of this benefit through 4 years of follow-up. We found no significant differences between drug-eluting stents and bare-metal stents in the rates of death or myocardial infarction.

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CLINICAL TRIAL REGISTRATION

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Late Clinical Events After Clopidogrel Discontinuation May Limit the Benefit of Drug-Eluting Stents: An Observational Study of Drug-Eluting Versus Bare-Metal Stents

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EXPEDITED REVIEWS

Late Clinical Events After Clopidogrel Discontinuation May Limit the Benefit of Drug-Eluting Stents

An Observational Study of Drug-Eluting Versus Bare-Metal Stents

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OBJECTIVES We sought to define the incidence of late clinical events and late stent thrombosis in patients treated with drug-eluting (DES) versus bare-metal stents (BMS) after the discontinuation of clopidogrel as well as their timing and outcome.

BACKGROUND There is growing concern that delayed endothelialization after DES implantation may lead to late stent thrombosis and related myocardial infarction (MI) or death. However, event rates and outcomes after clopidogrel discontinuation versus BMS are unknown.

METHODS A consecutive series of 746 nonselected patients with 1,133 stented lesions surviving 6 months without major events were followed for 1 year after the discontinuation of clopidogrel. Patients were assigned randomly 2:1 to DES versus BMS in BASKET (Basel Stent Kosten Effektivitäts Trial). The primary focus of this observation was cardiac death/MI.

RESULTS Rates of 18-month cardiac death/MI were not different between DES and BMS patients. However, after the discontinuation of clopidogrel (between months 7 and 18), these events occurred in 4.9% after DES versus 1.3% after BMS implantation. Target vessel revascularization remained lower after DES, resulting in similar rates of all clinical events for this time period (DES 9.3%, BMS 7.9%). Documented late stent thrombosis and related death/target vessel MI were twice as frequent after DES versus BMS (2.6% vs. 1.3%). Thrombosis-related events occurred between 15 and 362 days after the discontinuation of clopidogrel, presenting as MI or death in 88%.

CONCLUSIONS After the discontinuation of clopidogrel, the benefit of DES in reducing target vessel revascularization is maintained but has to be balanced against an increase in late cardiac death or nonfatal MI, possibly related to late stent thrombosis. (J Am Coll Cardiol 2006;48: 2584–91) © 2006 by the American College of Cardiology Foundation

Drug-eluting stents (DES) are more effective than bare-metal stents (BMS) in reducing restenosis and related target vessel revascularization (TVR) (1–6), mainly by limiting intimal hyperplasia (7), with similar rates in death or nonfatal myocardial infarction (MI). However, concern is

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growing that delayed endothelialization, incomplete neointimal healing, or hypersensitivity reactions after the implantation of DES may lead to MI and death as the result of late stent thrombosis (8). The U.S. Food and Drug Administration even issued a warning in this regard (9). Although the incidence of subacute stent thrombosis was 1.0% to 1.5% within the first 30 days after stenting and <0.5% between 1 and 6 months without significant differences between patients treated with DES and BMS in randomized trials (10–13), there are only limited data on later events (13–15). One major reason for late stent thrombosis may be the reduction of dual antiplatelet therapy (15–17), which currently is recommended for 1 month after BMS, for 3 months after sirolimus-eluting stents, and for 6 months after paclitaxel-eluting stents (18). However, there remains widespread uncertainty regarding the risk of clinical events after the discontinuation of clopidogrel, particularly after DES implantation.

To address these questions, we prospectively followed a consecutive series of 746 nonselected patients randomized to DES versus BMS who survived the first 6 months after stenting without major clinical events and who stopped taking clopidogrel at that point in time. They initially were enrolled in the Basel stent cost-effectiveness trial, BASKET (Basel Stent Kosten-Effektivitäts Trial) (19). The specific

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Abbreviations and Acronyms

BASKET	= Basel Stent Kosten Effektivitäts Trial
BASKET-LATE	= BASKET LAte Thrombotic Events Trial
BMS	= bare-metal stent
CI	= confidence interval
DES	= drug-eluting stent
HR	= hazard ratio
MI	= myocardial infarction
OR	= odds ratio
TVR	= target vessel revascularization

aims of this prospective follow-up evaluation were to define the incidence of late clinical events and late stent thrombosis in DES- versus BMS-treated patients after the discontinuation of clopidogrel and to define predictors, timing, and outcome of such thrombotic events in relation to stent type implanted.

METHODS

Patient population and study design. Of a consecutive series of 988 patients treated with percutaneous coronary intervention and stenting between May 5, 2003, and May 31, 2004, at the University Hospital of Basel, Switzerland, 162 (16%) had to be excluded for a target vessel diameter of 4 mm or greater (largest DES size available 3.5 mm; n = 23), for presence of restenotic lesions (n = 49), and for no consent (mostly because of patient or referring physician preference for DES; n = 90), leaving 826 patients who were enrolled in BASKET (19). They were assigned randomly in a 2:1 fashion to DES versus BMS (i.e., 545 patients received DES) (Cypher Cordis, Johnson & Johnson, Miami Lakes, Florida, n = 264 or Taxus, Boston Scientific Corporation, Natick, Massachussetts, n = 281) and 281 patients a third-generation cobalt-chromium BMS (Vision, Guidant Corp., Indianapolis, Indiana) and were followed for death, nonfatal MI, and TVR. Target vessel revascularization was a clinical event because control angiography was not allowed without symptoms or signs of ischemia in this study. All 746 patients with a total of 1,133 stented lesions who survived the first 6 months without nonfatal MI or repeat TVR were enrolled in the present BASKET-LATE (BASKET LAte Thrombotic Events) study and followed for another 12 months (Fig. 1). Patients originated from the University Hospital of Basel and 4 affiliated hospitals without their own catheterization laboratory (see Appendix). This study was approved by the Ethics Committee of Basel, and each patient gave written informed consent.

Follow-up. After 18 months, all patients received a questionnaire with specific questions regarding rehospitalizations, adverse events, and drug therapy. Data of patients with repeat procedures were collected prospectively. Additional data were obtained from primary care physicians, referring cardiologists, patients, or relatives when necessary.

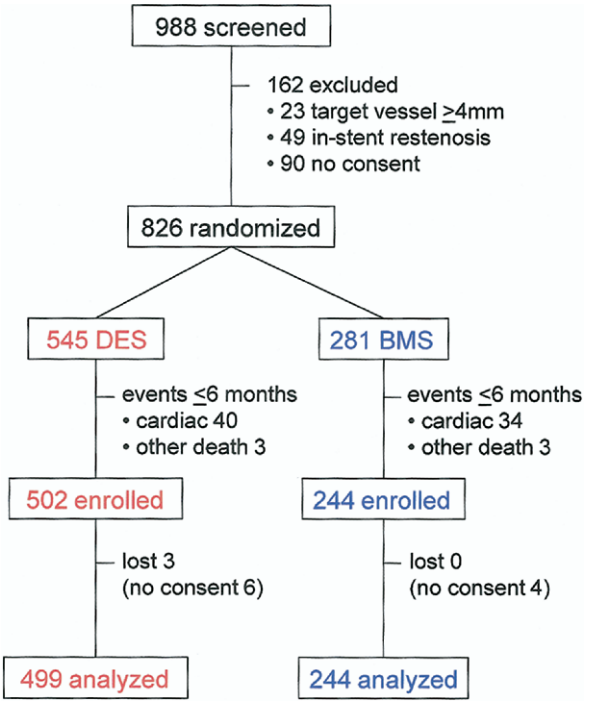

Figure 1. Patient flow chart. Note that 746 of 826 patients (90.3%) surviving the initial 6 months without major cardiac events were enrolled. Follow-up regarding survival was complete in 743 of 746 patients (99.6%), whereas 10 patients were alive and well but did not consent to detailed information. BMS = bare-metal stent; DES = drug-eluting stent.

Ten patients were alive and well but did not consent to follow-up questioning (they are included in survival analyses), whereas 3 had moved out of the country and could not be located. Thus, follow-up was complete in 743 of the 746 patients (99.6%) regarding survival and in 733 (98.3%) regarding all events (Fig. 1).

Angioplasty and antiplatelet therapy. Angioplasty was performed according to standard techniques with the final decision about the appropriate strategy in each patient left to the judgment of the physician in charge (19). All 157 patients presenting with ST-segment elevation MI were treated with primary angioplasty and all 273 patients with other acute coronary syndromes with urgent agioplasty within 24 h of presentation. All patients received a loading dose of 250 to 500 mg aspirin intravenously or orally and clopidogrel 300 mg orally. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the physician in charge, mainly given in patients with acute coronary syndromes, complex lesions, or suboptimal angioplasty results. All patients received a maintenance dual antiplatelet therapy with aspirin 100 mg and clopidogrel 75 mg daily for 6 months, irrespective of stent type used. In addition, in all patients long-term statin therapy was prescribed. Patients were advised to stop clopidogrel after 6 months but to continue 100 mg of aspirin daily long-term. Medication was recorded at follow-up and at the time of any event.

Definition of late events. For this study, "late" was defined as occurring between 7 and 18 months after stenting. Late clinical events, the focus of this observation, were any

cardiac death and documented nonfatal MI. Of these events, all sudden cardiac deaths and all MIs attributable to the target vessel were considered to be "thrombosis-related" (previously called "possible" thromboses) (11). Angiographically documented "definite" late stent thrombosis was defined as ischemic clinical event with angiographically proven stent thrombosis (i.e., Thrombosis In Myocardial Infarction [TIMI] flow 0 or 1 or the presence of flow-limiting thrombus [TIMI flow 1 or 2]). Target vessel revascularizations not related to thrombosis-related events were assumed to be "restenosis-related." Thus, major cardiac events were a composite of cardiac death, nonfatal MI, and TVR. All deaths not clearly due to other causes like cancer or suicide were considered to be cardiac. Nonfatal MI was diagnosed according to current guidelines (20). All these events were adjudicated by an independent clinical event committee blinded to the stent types used.

Statistics. All analyses were performed with the primary aim to compare patients with DES and BMS and to perform additional secondary exploratory analyses between the 2 DES used. Because this study was planned as follow-up investigation of BASKET, sample size calculations were performed for that purpose (19). Therefore, patients were followed in an "observational" manner, which did not allow formal statistical comparisons for the time period of month 7 to 18. Quantitative variables are presented as mean ± standard deviation or median ± interquartile ranges as appropriate. Categorical variables are described by their distribution. Two-group comparisons were performed using the Fisher exact test for categorical variables and unpaired *t* test or Mann-Whitney *U* test for quantitative variables. Kaplan-Meier curves were used for calculating time-dependent occurrences of events and the log rank test to compare DES and BMS. Predictors with a p value ≤0.1 were entered in a multivariate Cox-regression analysis adjusted to differences in baseline characteristics to test independence of these predictors. All calculations were performed with the use of a commercially available statistical package (version 13.0, SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics. Baseline characteristics of all 826 patients included in BASKET have been described previously (19). The baseline characteristics of patients surviving the first 6 months without major cardiac events did not differ between patients treated with DES and BMS apart from the total stent length and the use of small stents ≤2.5 mm (Table 1). This was true despite the fact that fewer patients treated with DES had such events during the first 6 months compared with patients treated with BMS (7.2% vs. 12.1%, p = 0.02) (19). Baseline characteristics reflect a relatively high-risk patient population presenting often with acute coronary syndromes and an extensive, complex coronary anatomy as seen in contemporary high-volume centers.

Late clinical events. After the discontinuation of clopidogrel, the rate of cardiac death or nonfatal MI between months 7 and 18 was low; however, all 6 cardiac deaths and 20 of 23 MIs (87%) occurred in patients who had received DES, resulting in a higher rate of cardiac death and nonfatal MI for DES compared with BMS-treated patients (Fig. 2). In contrast, the rate of restenosis-related TVR tended to be lower in DES patients, resulting in a comparable rate of major cardiac events for this time period (9.3% vs. 7.9%, DES vs. BMS, respectively).

To compare long-term effects, cumulative event rates were calculated during the whole follow-up period and apart from intervention-related early events (initial 30 days). Because the rate of procedure-related 30-day death and nonfatal MI were greater after BMS compared with DES (4.6% vs. 2.0%, p = 0.05, rather because of patient characteristics [acute MI patients]/chance than to stent type used [21] and certainly not to drug-effects of DES), the overall rate of cardiac death/nonfatal MI was not different between DES and BMS use for the entire 18-month period (8.4% vs. 7.5%, p = 0.63), but the rate of TVR remained lower (7.5% vs. 11.6%, p = 0.04) (Figs. 3A and 3B). Focusing on late events and excluding the early intervention-related hazard, rates of death and nonfatal MI were similar in both groups up to 6 months. However, although the curve flattened later on in patients receiving BMS, there was a constant increase during the entire period in these events after DES implantation (Fig. 3C). In multivariate analysis, DES was accompanied with a significantly increased risk for these events (hazard ratio [HR] 2.2, 95% confidence interval [CI] 1.1 to 4.7, p = 0.03). In contrast, the benefit of DES over BMS was maintained long-term for restenosis-related TVR (Fig. 3D). In multivariate analysis, DES nearly halved the risk of restenosis-related TVR (HR 0.52, 95% CI 0.33 to 0.85, p = 0.009).

Exploratory subanalyses showed that there were no significant differences between the 2 DES used in any of these analyses; however, this was not expected based on low event rates and sample sizes of these subgroups (18 months cardiac death/MI for Cypher, 7.2%; Taxus, 9.6%; p = 0.31).

Late thrombosis-related events. After the discontinuation of clopidogrel, 16 of 65 events (25%) were related to stent thrombosis: 3 cardiac deaths, 11 nonfatal MIs, and 2 angiographically proven subtotal thrombotic obstructions with increasing angina but no infarction. Late stent thrombosis was documented in one patient who died (the other 2 patients died suddenly without autopsy) and in 8 of 11 patients with MI. Figure 4 shows the incidence of these late thrombosis-related events in relation to the stent type implanted. Although differences were not significant in view of the relatively low overall frequencies, there was a 2- to 3-fold increased rate of such late events in DES- compared with BMS-treated patients. Importantly, however, these findings between DES versus BMS were consistent and congruent with the primary focus of this study.

Thrombosis-related events occurred after a median time of 116 (interquartile range 53 to 313) days after the

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Table 1. Baseline Characteristics

	Overall (n = 743)	DES (n = 499)	BMS (n = 244)
Age, yrs	63.6 ± 11.3	63.6 ± 11.3	63.5 ± 10.8
Male, n (%)	584 (78.6)	393 (78.8)	181 (78.3)
History, n (%)			
Diabetes	135 (18.3)	84 (16.9)	51 (21.1)
Hypertension	491 (66.5)	327 (66.1)	164 (67.5)
Hypercholesterolemia	569 (77.3)	383 (77.2)	186 (77.5)
Current smoking	209 (28.3)	133 (26.8)	76 (31.4)
Previous MI	203 (27.3)	137 (27.5)	66 (27.0)
Previous PCI	118 (16.1)	83 (16.6)	35 (14.3)
Previous CABG	92 (12.4)	66 (13.2)	26 (10.7)
Presentation, n (%)			
STEMI	157 (21.1)	105 (21.0)	52 (21.3)
Unstable	273 (36.7)	183 (36.7)	90 (36.9)
Stable	313 (42.3)	211 (42.3)	102 (41.8)
Coronary angiogram, n (%)			
Multivessel disease	496 (66.8)	332 (66.5)	164 (67.2)
LAD	382 (51.4)	260 (52.1)	122 (50.0)
LCX	230 (31.0)	154 (30.9)	76 (31.1)
RCA	261 (35.1)	177 (35.5)	84 (34.4)
Left main	8 (1.1)	3 (0.6)	5 (2.0)
Bypass graft	40 (5.4)	31 (6.2)	9 (3.7)
Baseline intervention			
Number of lesions	1,133	767	366
Glycoprotein IIb/IIIa blockers, n (%)	189 (25.7)	128 (25.7)	61 (25.0)
Stented segments per patient, n	1.5 ± 0.7	1.5 ± 0.7	1.4 ± 0.6
≥1 segments per patient, n (%)	307 (41.3)	214 (42.9)	93 (38.1)
≥1 segments ≤2.5 mm, n (%)	199 (26.8)	145 (29.1)	54 (22.1)
Stents per segment, n	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.5
Implanted stents per patient, n	1.9 ± 1.0	1.9 ± 1.1	1.8 ± 1.0
Stents ≤2.5 mm, n (%)*	199 (26.8)	145 (29.1)	54 (22.1)
Bifurcation lesions treated, n (%)	38 (5.1)	23 (4.6)	15 (6.1)
CTO treated, n (%)	26 (3.5)	13 (2.6)	13 (5.3)
Total stent length per patient, mm*	33 ± 20	34 ± 21	31 ± 19
Lesions with angiographic success, n (%)	712 (95.8)	480 (96.2)	232 (95.1)

*$p < 0.05$ BMS vs. DES.

BMS = bare metal stent; CABG = coronary artery bypass grafting; CTO = chronic total occlusions; DES = drug-eluting stent; LAD = left anterior descending; LCX = left circumflex; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction.

discontinuation of clopidogrel, with a wide range between 15 and 362 days (Fig. 5). Seven patients presented between months 7 and 9, 3 between months 10 and 12, and the remaining 5 between months 13 and 18. One event occurred on continued dual antiplatelet therapy (patient after previous coronary surgery and implantable cardioverter-defibrillator implantation for severe 3-vessel disease) and one 28 days after stopping aspirin as well.

Predictors of late thrombosis-related events. Patients with late thrombosis-related events after the discontinuation of clopidogrel differed at baseline from those without such events in that they had more previous MIs (56% vs. 27%, odds ratio [OR] 3.5, p = 0.01), an increased need for glycoprotein IIb/IIIa inhibitors (56% vs. 25%, OR 3.9, p = 0.006), more side branch occlusions (9% vs. 3%, OR 4.0, p = 0.05), and bypass graft stenting (25% vs. 5%, OR 6.3, p = 0.0001). Note that this analysis was performed in patients only after the discontinuation of clopidogrel (i.e., surviving the first 6 months without major adverse cardiac events), which may implicate a certain selection bias.

Outcome of late thrombosis-related events. Comparing presentation and outcome of the 16 thrombosis-related with the 49 other events during months 7 to 18 showed that in thrombosis-related events, cardiac mortality was somewhat higher (19% vs. 6%, p = 0.13) and the rate of nonfatal MIs significantly higher (75% vs. 22%, p ≤ 0.0001). Thus, thrombosis-related events carried a substantially increased risk of cardiac death or nonfatal MI compared with non-thrombosis–related events (88% vs. 27%, OR 19.4, p < 0.0001).

DISCUSSION

This prospective randomized comparison of DES versus BMS in a "real-world" setting shows for the first time that the incidence of late cardiac death or nonfatal MI after the discontinuation of clopidogrel is greater in DES- as compared with BMS-treated patients. Most of this difference was attributed to an increased rate of thrombosis-related events, which carried a much higher risk of cardiac death or

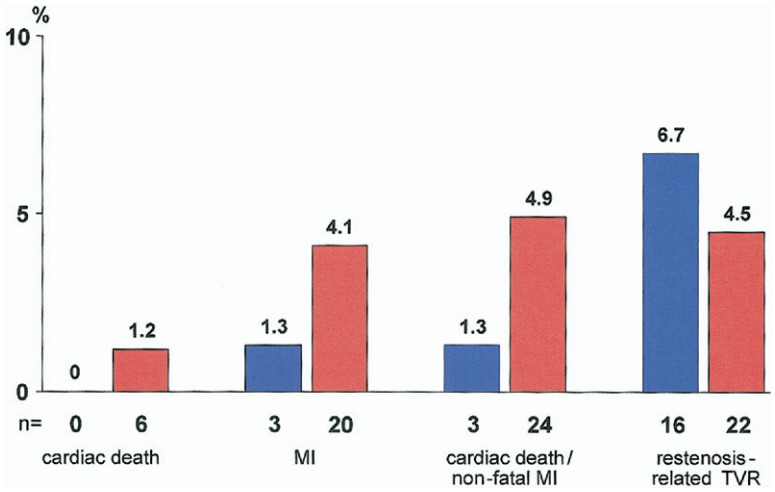

Figure 2. Late major cardiac events (months 7 to 18). Note that the primary focus of this observation, cardiac death or nonfatal myocardial infarction (MI), was significantly greater in drug-eluting stent **(red)** versus bare-metal stent **(blue)** groups, which contrasts with a trend toward a lower restenosis-related target vessel revascularization (TVR) rate after drug-eluting stents.

nonfatal MI than non-thrombosis–related events and occurred anytime between 15 and 362 days after the discontinuation of clopidogrel. Patients with a history of MI, the need for glycoprotein IIb/IIIa inhibitors at baseline, side-branch occlusions, or bypass graft stenting seemed to be at increased risk for such events. In contrast, there was a continued benefit of DES in reducing restenosis-related TVRs. These observational data suggest, therefore, that late clinical events possibly related to late stent thrombosis after the discontinuation of clopidogrel may limit the net clinical benefit of DES.

Late thrombotic stent occlusion. Late and sudden thrombotic coronary occlusion after percutaneous coronary interventions was first noted as a significant problem 2 to 15 months after brachytherapy (22). In contrast, meta-analyses of initial long-term outcomes after sirolimus-eluting (10,23) or paclitaxel-eluting stent implantation (12) pointed to the overall benefit of DES compared with BMS in selected patient groups and suggested no increased hazard of stent thrombosis compared with BMS use. However, there were case reports (8,16) demonstrating the occurrence of late stent thrombosis after DES implantation associated with a high risk of death or nonfatal MI. Reasons for thrombotic events were described in experimental (24) and autopsy studies (25): DES may delay endothelialization and impair intimal healing, partly in association with hypersensitivity

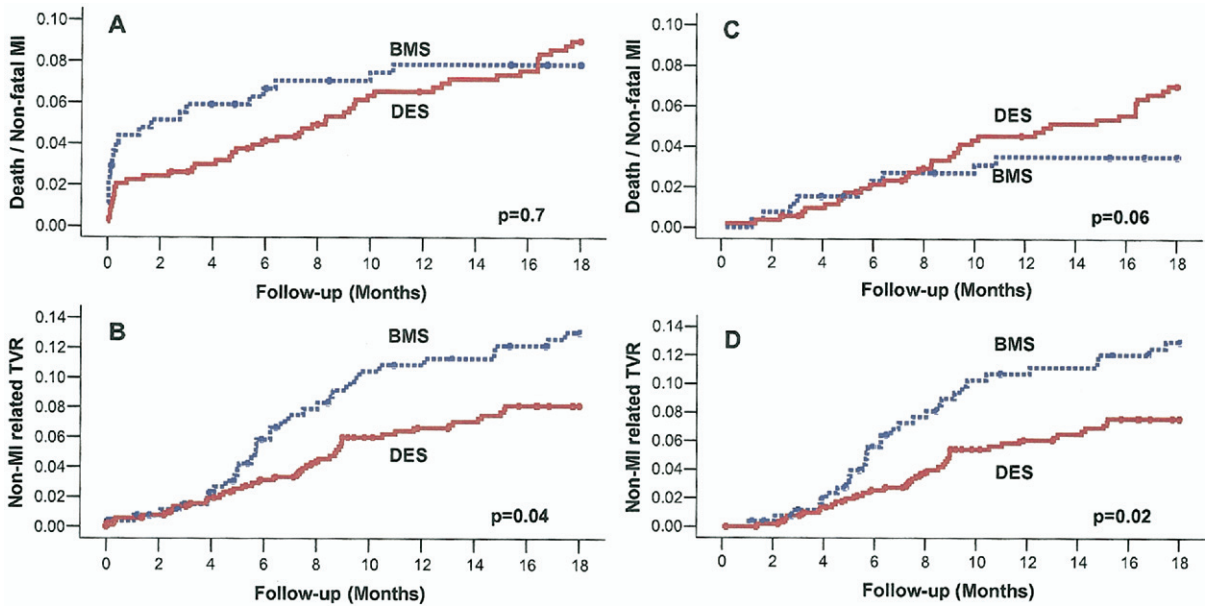

Figure 3. Cardiac death/myocardial infarction (MI) and restenosis-related target vessel revascularization (TVR) after drug-eluting (DES) versus bare-metal stent (BMS) implantation. Comparison of the occurrence of cardiac death/nonfatal MI **(A and C)** and the need for "restenosis-related" target vessel revascularization (TVR, **B and D**) after DES **(red)** versus BMS **(blue)** implantation. Note that in this graph, the initial 30-day events that are not related to drug-eluting properties of the stents are included (**A and B**, period 0 to 18 months) or disregarded (**C and D**, period 1 to 18 months).

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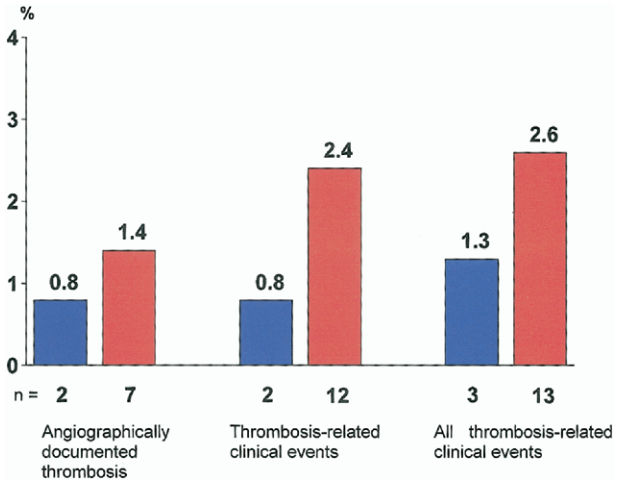

Figure 4. Late stent thrombosis and related clinical events. Late angiographically documented stent thrombosis and thrombosis-related clinical events for drug-eluting **(red)** versus bare-metal **(blue)** stent-treated patients. Note the overall low rates with formally nonsignificant differences but consistent findings of these events.

and inflammatory reactions, and thereby extend the time window during which stents are prone to thrombosis (8). This has been confirmed recently by angioscopic findings (26). Two large cohort-studies on >2,000 patients each analyzed their data for late angiographic stent thrombosis after DES implantation and reported an incidence of up to 0.7% during a follow-up duration of 9 and 18 months, respectively (13,15). Events occurred between 2 and 26 months, with case fatality rates of 29% and 45%. In the present report, rates of late angiographically documented stent thrombosis and thrombosis-related clinical events were even greater (1.6% and 2.6%, respectively). However, BASKET-LATE differs from previous such trials: late follow-up data were collected prospectively, more complex lesions were treated, almost 60% patients had acute coronary syndromes (one-third of them with ST-segment elevation myocardial infarction, 26% treated acutely with glycoprotein IIb/IIIa inhibitors), and clopidogrel was discontinued in all patients after 6 months with no protocol-driven control angiograms allowed and therefore no angiogram-driven repeat TVRs performed. In fact, several of these high-risk characteristics of the BASKET population turned out to be predictors of late thrombosis-related events, among them stenting of bifurcation or bypass-graft lesions. In contrast, the rate of clinically driven late restenosis-related TVRs remained lower after DES versus BMS. Of clinical relevance for the patient, however, is the "price" to pay (i.e., the high rate of cardiac deaths or nonfatal MI associated with late thrombosis-related events).

Implications of BASKET-LATE findings. The findings of BASKET-LATE may have major clinical implications. First, when using an antiplatelet regime as currently recommended and applied in BASKET/BASKET-LATE, one has to balance the benefit of the lower rate of reinterventions after DES implantation with the cost of an increased rate of late, presumably thrombosis-related, death or nonfatal MI compared with BMS use. In nonselected patients, implantation of DES may avoid 5 major cardiac events at 6 months in 100 patients treated (19) but lead to 3 patients suffering cardiac death or nonfatal MI during months 7 to 18. Second, one may speculate whether prolonged dual antiplatelet therapy may be beneficial as suggested after brachytherapy (27) and BMS implantation (28). However, the wide time window in which these thrombotic events occur, as noted in this study and in registry data by Ong et al. (15), may question a direct relation of clopidogrel discontinuation with these events, although clopidogrel withdrawal may even be associated with proinflammatory and prothrombotic effects in diabetic patients (29). In addition, the bleeding risk of prolonged dual antiplatelet therapy of up to 2% per year (30,31) and the increased cost would have to be taken into account. Therefore, such a prolonged dual antiplatelet therapy may only be justified in patients at increased risk for such events (13,15,32). Third, new strategies to reduce late thrombosis-related events have to be searched for; they may consist of other antiplatelet regimes, other stent types (e.g., bioabsorbable or endothelialization promoting stents) (33) or other drugs/drug dosages or drug release kinetics of DES. It may also be important to identify individual patient factors such as aspirin (34) or clopidogrel resistance (35), or

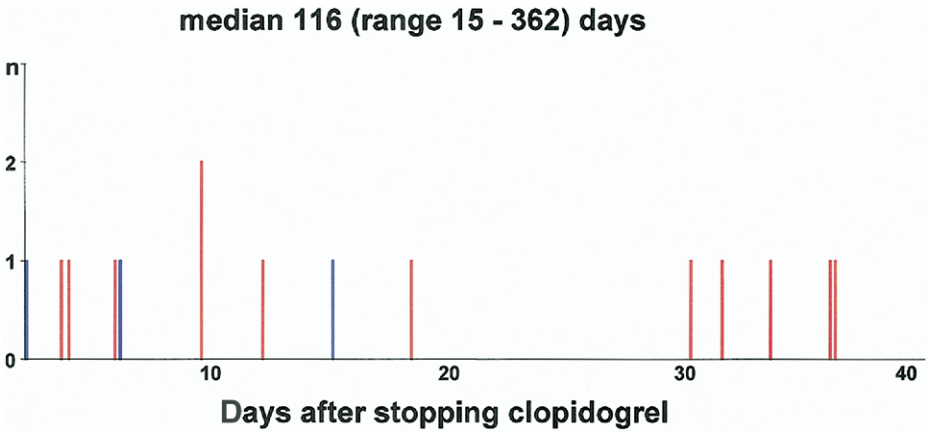

Figure 5. Timing of late thrombotic events after clopidogrel discontinuation. **Red** = drug-eluting stent; **blue** = bare-metal stent.

drug-drug interactions (36) and to treat affected patients specifically.

Study limitations. A major limitation of this study lies in the fact that power calculations were not based on the hypothesis of this study. Therefore, the data remain observational. In view of previous observations (14,15) and a meta-analysis of 4 randomized sirolimus-eluting stent trials with up to 3 years' follow-up (37), the expected incidence of late stent thrombosis was up to 0.3% for BMS and up to 0.9% for DES after the first year resulting in an estimated sample size of >6,000 patients needed to reach statistical significance. Although the present observational data suggest a somewhat-greater rate of these events, such a large study of nonselected patients randomized to DES versus BMS will hardly be performed to address this question, today.

Conclusions. This study highlights the clinical relevance of a relatively new phenomenon, late clinical events possibly related to late stent thrombosis, which seems to be of particular importance after DES implantation. It could not prove that thrombosis-related events were significantly more frequent after DES compared with BMS; however, the consistency of the findings within BASKET-LATE and with the marked difference in "hard" events, late death or MI, together with similar directional observations in previous randomized studies of selected patient groups underline the potential relevance of this observation. Although findings suggest a relation to discontinuation of dual antiplatelet therapy, this study gave no proof for a direct cause-effect relationship nor that thrombosis-related events could be prevented by such a therapy. Still, such a strategy may be chosen empirically, at least for patients at increased risk for such events, until better strategies to prevent late thrombosis-related events have been found and shown to be effective. In any case, physicians and patients should be alerted to this potential late harm of DES use.

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APPENDIX

BASKET/BASKET-LATE Hospitals and Investigators

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Critical Events Committee: P. Rickenbacher (chair), P. Hunziker, C. Mueller.

Secretarial assistance: E. Stalder, U. Vogt.

Late Clinical Events After Clopidogrel Discontinuation May Limit the Benefit of Drug-Eluting Stents: An Observational Study of Drug-Eluting Versus Bare-Metal Stents

Matthias Pfisterer, Hans Peter Brunner-La Rocca, Peter T. Buser, Peter Rickenbacher, Patrick Hunziker, Christian Mueller, Raban Jeger, Franziska Bader, Stefan Osswald, Christoph Kaiser, for the BASKET-LATE Investigators

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Hot Lines and Clinical Trial Updates

Session Number : 707009
Session Title: Hotline I
Core syllabus topic : Acute Coronary Syndromes (ACS)

Date : 3 September 2006

Reported by :
Camenzind
Discussant: Nordmann, A.J.

Safety of drug-eluting stents: insights from meta analysis.

A meta-analysis of first generation drug eluting stents - including both first generation drug eluting stent extent of both mortality and Q-wave Myocardial Infarction in comparison to bare metal stents. Here the presenter Edoardo Camenzind (Geneva, Switzerland) and the discussant Alain Nordmann (Basel, Switzerland) provide an overview of the results.

Introduction

First generation drug eluting stents (1stg-DES: sirolimus eluting stent [SES] have been widely accepted and are used for a large spectrum of clinical indications.

Recently case reports and autopsy reports have been published on single cases as well as on series of cases which experienced stent thrombosis more than 30 days after stent deployment, so called late stent thrombosis. Delayed healing and diminished antiplatelet therapy could be demonstrated as relevant precipitating factor.

The global incidence of 'in-1st g-DES' thrombosis according to the literature remains uncertain. According to some single center registries and post-marketing surveyance registries as well as meta-analysis the incidence of late angiographic stent thrombosis does not seem to be higher in 1st g-DES as compared to bare metal stents (BMS). However according to the recently presented BASKET-Late trial, a small randomized trial designed to evaluate cost effectiveness of 1st g-DES versus BMS, severe cardio-vascular events were significantly higher in patients with 1st g-DES as compared to BMS in the year following the interruption of dual antiplatelet therapy.

Methods

The current analysis embraced both 1st g-DES clinical programs (SES and PES) and included all available data concerning company supported randomized double-blind clinical trials comparing 1st g-DES to the respective BMS control. Of the SES program the following trials were included: RAVEL, SIRIUS, E-SIRIUS and C-SIRIUS and for the PES program: TAXUS II, IV, V and VI accounting for a total of n=878 SES vs n=870 BMS and n=1685 PES vs n=1675 BMS. Available randomized trials' data within a specific study program (SES or PES) were stratified by trials and data of the same time-periods of follow-up were pooled as well as data of the latest available follow-up.

The clinically oriented analysis focuses on death, Q-wave MI and death and Q-wave MI combined thought to reflect the incidence of stent thrombosis best instead of using restrictive thrombosis definitions (e.g. late angiographic stent thrombosis).

Results

The incidence - up to the latest available follow-up - of total mortality and Q-wave MI combined were 38% (SES) and 16% (PES) higher in 1st g-DES as compared to control BMS (p-value: SES vs BMS: 0.03 ; PES vs BMS. 0.68).

Conclusion

**Antiplatelet (a
aspirin) therap
is relatively
inefficacious in
high risk patie
with Atrial
Fibrillation**

I agree
I disagree

Death and Q-wave myocardial infarction have a higher incidence in 1st generation drug eluting stents as compared to the bare metal control stents.

Thus the indiscriminated use of 1st g-DES should be avoided and the use of bare metal stent may still be maintained awaiting for safer 2nd g-DES.

DISCUSSANT: Nordmann, A.J.

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